REMARKS

Claims 1-22 are pending in the application. Claims 1-22 have been cancelled without prejudice or disclaimer to applicants' right to pursue patent protection for the subject matter of those claims in a subsequent application. Proposed new claims 23-45 are submitted for entry into the application. These claims are directed to the same invention as claims 1-22 and they are completely supported by the application as originally filed. Thus they raise no issue of new matter. In particular, support for new claims 23-45 may be found in the specification as follows: **Claim 23**: page 4, lines 2-10, page 96, lines 19-22 and original claim 1; **Claim 24**: page 4, lines 2-10, page 10, lines 4-15, page 96, lines 19-22, Figures 3 and 6d and original claim 1; **Claim 25**: corresponds to original claim 2; **Claim 26**: corresponds to original claim 3; **Claim 27**: corresponds to original claim 4; **Claim 28**: corresponds to original claim 5; **Claim 29**: corresponds to original claim 6; **Claim 30**: corresponds to original claim 7; **Claim 31**: corresponds to original claim 8; **Claim 32**: corresponds to original claim 9; **Claim 33**: corresponds to original claim 10; **Claim 34**: corresponds to original claim 11; **Claim 35**: corresponds to original claim 12; **Claim 36**: corresponds to original claim 13; **Claim 37**: corresponds to original claim 14; **Claim 38**: corresponds to original claim 15; **Claim 39**: corresponds to original claim 16; **Claim 40**: corresponds to original claim 17; **Claim 41**: corresponds to original claim 18; **Claim 42**: corresponds to original claim 19; **Claim 43**: corresponds to original claim 20: **Claim 44**: corresponds to original claim 21; and **Claim 45**: corresponds to original claim 22.

Applicants respectfully request that the Examiner enter the present Amendment containing new claims 23-45 into the file of the application because the new claims, which as noted are

completely supported by the application as filed, are believed to place the application in condition for allowance, or at a minimum to significantly reduce the issues for an appeal.

In reviewing the specification of their application during the preparation of this Amendment, applicants noted that several locations in the specification (i.e., pps. 50-56 and p. 82) contained typographical errors in the identification of the Figures cited to therein. Thus applicants have amended the specification as indicated below to correct these obvious typographical errors. These amendments are all supported by the application as originally filed and thus they add no new matter to the application.

In particular, on page 50, at line 15, --Figure 1-- was mis-identified as "Table 1", i.e., there is no "Table 1" in the application and thus clearly "Figure" 1 was intended. The same correction was made on line 1 at page 51. On page 52, at lines 9, 18 and 28, "Figure 1" was corrected to read --Figure 4--. It is readily apparent from the accompanying text that Figure 4 is the appropriate figure. On page 53, at line 14, "Fig. 2a" was corrected to read --Fig. 5a--, at line 21, "Fig. 2a, b" was corrected to read --Fig. 5a, b-- and on lines 23-24, "Fig. 2b" was corrected to read --Fig. 5b--. The application contains only a single Figure 2, i.e., there is no Fig. 2a or 2b. It is apparent from the accompanying text that applicants intended to identify Figs. 5a and b. On page 54 of the application, on line 5, "Fig. 3a" was corrected to --Fig. 6a-, i.e., the application contains only a single Figure 3 and there is no Fig. 3a. At lines 7-8 and line 24 on page 54, "Table 3" was corrected to --Figure 3--, i.e., there is no Table 3 in the application and "Figure" 3 was clearly intended. On page 54 at line 18, "Fig. 3b" was corrected to read --Fig. 6b--. Further, on page 55 of the

application: at line 5, "Fig. 3c" was corrected to --Fig. 6c--; at line 8, "Fig. 3d" was corrected to --Fig. 6d--; at line 10, "Table 1" was corrected to --Figure 1--; and on lines 13 and 16, "Table 3" was corrected to --Figure 3--. On page 56 of the specification, on lines 11-12, "Figure 4 and Table 2" was corrected to --Figure 7 and Figure 2--. On lines 28-29 and 35, "Table 2" was corrected to --Figure 2--. On line 31, "Fig. 2a, b" was corrected to --Fig. 5a, b-- (again, there is only a single Figure 2 filed in the application). Finally, on page 82 of the specification, at line 14 "Figure X" was corrected to --Figure 10-- (Roman Numeral "X" = 10). All of the above corrections are supported by the application as originally filed and thus they do not raise any issue of new matter. Entry of these amendments into the file of the application is therefore respectfully requested.

Applicants acknowledge with appreciation the Examiner's statement on page 2 of the Office Action that the CRF has been entered and is acceptable.

Applicants also acknowledge the Examiner's statement on page 2 of the Office Action that the rejection of claims 5-10 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant[s] regards as the invention is withdrawn in view of applicants' amendment.

Applicants further acknowledge the Examiner's statement on page 2 of the Office Action that the rejection of claims 1-10, 21 and 22 under 35 U.S.C. §102 (a) as being anticipated by Olson et al. (WO 00/35409) is withdrawn in view of applicants' arguments.

Applicants additionally acknowledge the Examiner's statement on

page 2 of the Office Action that the rejection of claims 1, 2 and 5-10 under 35 U.S.C. §102 (b) as being anticipated by Vila-Coro et al. (PNAS 3/00) is withdrawn in view of the amendment to the claims.

Finally, applicants acknowledge the Examiner's statement on page 3 of the Office Action that the rejection of claims 1-22 under 35 U.S.C. §103 (a) as obvious over Olson et al. (WO 00/35409) is withdrawn in view of applicants' arguments.

The Examiner has stated, however, on page 3 of the Office Action, that the rejection of claims 1-22 under 35 U.S.C. §103 (a) as obvious over Vila-Coro et al. (PNAS 3/00) is maintained. The Examiner further stated that the rejection is based on new grounds, as follows, necessitated by applicants' amendment.

The Examiner stated that applicant has amended the claimed invention to providing the treatment solely after HIV-1 infection. The Examiner stated that this obviates the §102 rejection but the claimed invention is obvious in view of the reference. The Examiner stated that contrary to applicant's arguments, the process as now claimed and as taught by the reference is not significantly different. The Examiner stated that applicants argue that there is no evidence in the reference as to whether pre- or post-infection treatment was responsible for the efficacy. The Examiner stated that this is not convincing as the process of HIV-1 infection, as applicants are aware, is a steady onslaught of fresh infections of uninfected T-cells until the immune system is overwhelmed and the patient succumbs to illness. The Examiner stated that, put another way, a fulminant infection requires a continuous supply of uninfected cells that replace the infected cells that die-off which are in turn fresh victims of HIV-1 infection. The Examiner stated that thus,

infection is a process of continual infection. The Examiner stated that the mechanism of infection is the same whether it is the very first occurrence of the infection in a subject or a later infection of a T-cell in the subject. The Examiner stated that given the prior art knowledge that the co-receptor is required to allow HIV-1 to enter a susceptible cell, it would be obvious to the artisan that blocking the co-receptor would be efficacious at any stage. The Examiner stated that therefore, one would not exclude post-infection treatment. The Examiner stated that thus, the instant invention is obvious over Vila-Coro et al.

Applicants respectfully traverse the rejection of claims 1-22 under 35 U.S.C. §103 (a) over Vila-Coro et al. ("Vila-Coro") for the reasons which follow.

As noted above, applicants are submitting herewith proposed new claims 23-45 to replace original claims 1-22. These new claims 23-45 are directed to the same invention as claims 1-22. The subject claims define the invention in a manner which completely distinguishes it over the Vila-Coro reference.

As recited, for example, in new claim 23, the invention is directed to a method of reducing HIV-1 viral load in an HIV-1 infected subject which comprises administering to the subject solely after viral steady state is reached an effective viral load-reducing amount of an antibody which (a) binds to a CCR5 chemokine receptor and (b) inhibits fusion of HIV-1 to a CD4+CCR5+ cell, so as to thereby reduce the subject's HIV-1 viral load to 50% or less of the subject's viral load prior to any administration of the antibody to the subject.

In a further embodiment, as recited in new claim 24, the invention is directed to a method of reducing HIV-1 viral load in

an HIV-1 infected subject which comprises administering to the subject an effective viral load-reducing amount of an antibody which (a) binds to a CCR5 chemokine receptor, (b) inhibits fusion of HIV-1 to a CD4+CCR5+ cell, and (c) inhibits binding of $HIV\text{-}1_{JR\text{-}FL}$ gp120 to the CCR5 receptor, so as to thereby reduce the subject's HIV-1 viral load to 50% or less of the subject's HIV-1 viral load prior to any administration of the antibody to the subject.

In contrast to the invention as now claimed, the Vila-Coro reference describes a prophylactic treatment regimen which involves treating a group of SCID mice both pre- and within two days post- infection. That is, as stated for example on p. 3389, col. 2, lines 16-18:

Four hours before viral challenge and on the next two days, mice were injected i.p. with purified CCR5–02 mAb or an isotype-matched mAb (200 μg/mouse) in PBS.

That is, as pointed out in applicants' Amendment In Response To June 25, 2002 Office Action filed December 30, 2002, in the process described by Vila-Coro, *uninfected* (i.e., with HIV) animals were initially pre-treated with a prophylactic dose of the CCR5 receptor-specific mAb. These *pre-treated* animals were only exposed to the HIV virus after such antibody treatment, following which they were *again* treated on two consecutive days following the viral challenge, i.e., for a *second and third* time, with the antibody in an effort to reduce their viral load.

In contrast new claim 23 specifically recites that the method of the present invention involves reducing viral load in an HIV-1-infected subject (which clearly excludes the treatment of subjects yet to be challenged by the virus) by administering the antibody to the subject *solely after a viral steady state is*

reached. As exemplified by applicants using the SCID mouse model, the viral steady state was reached about 8 to 10 days post-infection (page 96, lines 19-22 of the specification). Contrasting the claimed method to that disclosed in the subject Vila-Coro reference, the SCID mice treated as described by the reference have not achieved a viral steady state either (1) four hours before the viral challenge, or (2) within only two days after such challenge. The Vila-Coro reference is thus describing the treatment of an acute infection in newly infected subjects, whereas the present invention is directed to the treatment of chronic, established infections, i.e., in subjects wherein a viral steady state has been reached. Thus the method recited in new claim 23 is clearly distinguishable over that described in the Vila-Coro reference.

Further to the above, as applicants established in their previous response through the submission of the Poignard, et al. ("Poignard") and Gauduin et al. ("Gauduin") references, antibodies may be useful in *preventing* infection when administered prior to challenge by a virus (i.e., the pre-treatment setting disclosed in Vila-Coro), while providing a limited degree of protection, or none at all, when administered after infection has taken place.

In particular, Poignard discloses the administration of, *inter alia*, the IgG1b12 antibody, i.e., "b12", disclosed for use in the Vila-Coro reference. According to the authors of the reference:

> Neutralizing antibodies can protect against challenge with HIV-1 in vivo if present at appropriate concentrations at the time of viral challenge, but any role in the control of established infection is unclear (see Summary, p.431).

The authors went on to state (at p. 434, col. 2) that:

In order to study the impact of neutralizing Abs on an ongoing HIV-1 infection, we have administered potent neutralizing Abs to HIV-1 infected hu-PBL-SCID mice after the infection had been established for some days, in most cases when the viral load had reached steady-state levels. Our results show that passive administration of either a single neutralizing human mAb or of a cocktail of three such Abs has minimal effect on the control of an ongoing HIV-1 infection in the hu-PBL-SCID mouse model.

Turning next to the Gauduin reference, although the IgG1b12 antibody was found to block infection when administered after HIV-1 challenge, this effect was obtained only when the antibody was administered no more than several hours after viral exposure, i.e., significantly before viral steady state is reached. In contrast, claim 23 recites, as noted above, that the HIV-1 viral load of the HIV-1-infected subject is reduced when the antibody is administered "solely after viral steady state is reached."

The Poignard and Gauduin references thus clearly support applicants' contention that antibodies useful for prophylactic treatment when administered prior to infection often do not protect against an established HIV-1 infection. Thus, based on the prior art teachings of Poignard and Gauduin, one skilled in the art at the time the invention was made could not have predicted and certainly would not have had an expectation that treatment administered solely after viral steady state had been reached would be efficacious.

As previously noted by applicants in their prior response, the Vila-Coro reference provides no teaching as to how to determine whether the viral reduction noted therein is due (a) to the pre-treatment of the uninfected animals with the antibody four hours prior to challenge, (b) to the subsequent treatment of the infected animals with the antibody on two consecutive days following challenge, or (c) some combination of these two

treatment regimens. Moreover, there is no teaching or suggestion in the Vila-Coro reference to abandon or modify the treatment regimen provided therein, i.e., prophylactic treatment four hours prior to viral challenge followed by two consecutive days of treatment after viral challenge. The invention as recited, *inter alia*, in new claim 23 would thus not be obvious to one of ordinary skill in this art over the disclosure of the Vila-Coro reference.

Applicants' other proposed independent claim, i.e., no. 24, recites the invention in a somewhat different manner. Claim 24 recites that the method involves administering to the subject an effective viral load-reducing amount of an antibody which, *inter alia*, inhibits binding of HIV-1_{JR-FL} gp120 to the CCR5 receptor. The antibody used in Vila-Coro, however, does not interfere with the R5 JR-FL viral strain gp120 binding to CCR5. As stated, for example, on p. 3392, col. 1, last paragraph of the Vila-Coro reference:

> The CCR5-02 mAb . . . is the only mAb that recognizes an epitope not primarily implicated in HIV-1 infection [citations omitted], that does not interfere with chemokine or gp120 binding, yet blocks viral infection.

As further stated on p. 3388 of the reference in col. 2, second paragraph, the subject antibody, "[d]oes not affect the binding of R5 JRFL viral strain gp120."

As demonstrated above, therefore, the invention as recited in new claim 24 (as well as in claim 23) is completely distinguishable over the disclosure of the Vila-Coro reference. Furthermore, new claims 25-45 all depend, directly or indirectly, on claims 23 and 24 and thus these claims are believed to be distinguishable over Vila-Coro for the same reasons as claims 23-24. The Examiner is therefore respectfully requested to reconsider and withdraw the

rejection of the claims under 35 U.S.C. §103(a) based on the Vila-Coro reference.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examine to telephone either of them at the number provided below.

A fee of SIX HUNDRED FOURTEEN DOLLARS is deemed necessary in conjunction with the filing of this response. This fee includes $465.00 for a three month extension of time, plus $140.00 for the addition of multiple dependent claims 23 and 24 into the application, plus a further $9.00 due for the inclusion of an additional dependent claim, i.e., new claims 23-45 amount to 23 claims, one more claim than the 22 claims that were originally filed ($465 + $140 + $9 = $614.00). A check for the indicated amount is enclosed. If any additional fee is due, authorization is hereby given to charge the required fee to Deposit Account No. 03-3125.

Respectfully submitted,

Mark A. Farley

John P. White
Registration No. 28,678
Mark A. Farley
Registration No. 33,170
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Mark A. Farley 8/21/03

John P. White Date
Reg. No. 28,678
Mark A. Farley
Reg. No. 33,170